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Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis

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Abstract

Objective/Design: Menopausal transition has been associated with a derangement of glucose metabolism. However, it is not known if early menopause (EM, defined as age at menopause <45 years) or premature ovarian insufficiency (POI, defined as age at menopause <40 years) are associated with increased risk of type 2 diabetes mellitus (T2DM). To systematically investigate and meta-analyze the best evidence regarding the association of age at menopause with the risk of T2DM.

Methods: A comprehensive search was conducted in PubMed, CENTRAL and Scopus, up to January 31st, 2018. Data were expressed as odds ratio (OR) with 95% confidence intervals (CI). The I^2 index was employed for heterogeneity.

Results: Thirteen studies were included in the qualitative and quantitative analysis (191,762 postmenopausal women, 21,664 cases with T2DM). Both women with EM and POI were at higher risk of T2DM compared with those of age at menopause of 45-55 years (OR: 1.15, 95% CI: 1.04-1.26, p=0.003; I^2: 61%, p<0.002 and OR: 1.50, 95% CI: 1.03-2.19, p=0.033; I^2: 75.2%, p<0.003), respectively). Similar associations emerged when women with EM and POI were compared with those of age at menopause >45 years (OR: 1.12, 95% CI: 1.01-1.20, p<0.02; I^2: 78%, p<0.001 and OR: 1.53, 95% CI: 1.03-2.27, p=0.035; I^2: 78%, p<0.001), respectively).

Conclusions: Both EM and POI are associated with increased risk of T2DM.

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Introduction

Menopause is chronically determined by the completion of 12 months after the final menstrual period. It is the consequence follicular depletion leading to estrogen deficiency [1]. The average age at menopause is 50-52 years [2]. However, approximately 10% of the female population enter menopause before 45 years, a condition termed "early" or "premature" menopause [3]. About 1% of women enter menopause under the age of 40 (0.1% under the age of 30), a condition termed "premature ovarian insufficiency" (POI) [3, 4]. Except of the vasomotor symptoms affecting the woman's quality of life, transition to menopause has been also associated with a potential higher cardiovascular (CVD) risk, mainly attributed to a more atherogenic lipid profile, central adiposity and glucose intolerance [5-8].

Both early menopause (EM) and POI have been associated with increased risk of death and CVD in recent meta-analyses [9, 10]. With respect to glucose metabolism, the true effect of endogenous hormonal milieu during menopause on T2DM risk is controversial, since some, but not all, studies have shown a possible association between EM and increased risk of T2DM [11-14]. The association of T2DM with increased CVD risk has been well-documented in both genders, although women with T2DM seem to be at a higher relative CVD risk compared with their male counterparts [15]. However, whether EM or POI *per se* is associated with increased risk of T2DM is unknown.

The aim of this study was to systematically investigate and meta-analyze the best evidence regarding the association of menopausal age with the risk of developing T2DM.

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Subjects and methods

Guidelines followed

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [16]. A flow diagram is available in Figure 1. A completed PRISMA checklist is available as Supplementary Table 1.

Search strategy

The following PICO (Population, Intervention or exposure, Comparison, Outcome) elements were applied as inclusion criteria for the systematic review: (i) Population: postmenopausal women; (ii) Intervention: early age at menopause, either EM or POI; (iii) Comparison group: women with natural menopause; (iv) Outcome: T2DM. To identify eligible studies, the main search was conducted in the electronic databases MEDLINE, Scopus and Cochrane (CENTRAL) covering the period from conception until 31st January 2018 and using the following search strings: ("menopause, premature"[MeSH] OR "primary ovarian insufficiency"[MeSH] OR “ovarian insufficiency”[tiab] OR “ovarian failure”[tiab] OR ((menopause[MeSH] OR menopause[tiab] OR menopausal[tiab] OR climacteric[tiab] OR postmenopausal[tiab] OR post-menopausal[tiab]) AND (early[tiab] OR premature[tiab] OR age[tiab] OR years[tiab] OR time[tiab]))) AND ("diabetes mellitus, Type 2"[MeSH] OR (diabet*[tiab] AND (“non-insulin dependent”[tiab] OR “non-insulin-dependent”[tiab] OR type-2[tiab] OR “type 2”[tiab] OR “type II”[tiab])) OR diabetes[ti] OR diabetic[ti]) NOT (Animal[MeSH] NOT Human[MeSH]) NOT (letter[pt] OR comment[pt] OR editorial[pt] OR Review[pt] OR "practice guideline"[ptyp] OR "case reports"[ptyp]). The main search was completed

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independently by two investigators (KC and AMA). Any discrepancy was solved by consultation of an investigator, not involved in the initial procedure (PA and DGG).

Trial selection

Specific inclusion criteria were set as follows: (i) Studies conducted in postmenopausal women (either hysterectomized or non-hysterectomized), and (ii) Studies providing extractable data. Both cohorts and case-control studies were eligible. Studies were excluded if they: (i) Had no control group (without T2DM); (ii) Their population included pre- or peri-menopausal women; (iii) Included subjects receiving concomitant therapy with drugs affecting glucose metabolism, such as glucocorticoids; (iv) Were written in a language other than English; (v) Included patients with genetic syndromes associated with EM or POI (e.g. Turner's syndrome); (vi) Included women with a history of polycystic ovarian syndrome (PCOS), and (vii) Were conducted in animals.

Data extraction

Two researchers (KC and AMA) reviewed all eligible studies. The following data were extracted and recorded: (i) First author; (ii) Year of publication; (iii) Country in which the study was conducted; (iv) Study design (case-control or cohort); (iv) Duration (available in cohorts); (v) Total number of participants; (vi) Number of women with EM; (vii) Number of women with POI; (viii) Number of women with normal menopause (subdivided in those with menopausal age between 45 and 55 years and those with a menopausal age >45 years; (ix) Number of women with late menopause (>55 years); (x)

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Number of cases with T2DM in each of these categories. Parameters such as mean age of the participants at study entry, mean body mass index (BMI), the percentage of women with surgical menopause, the method of T2DM diagnosis, smoking status and physical activity were also recorded.

The following comparisons were made according to the incidence or prevalence of T2DM: (i) Women with EM compared with those with menopausal age of >45 years; (ii) Women with EM compared with those with menopausal age of 45-55 years; (iii) Women with POI compared with those with menopausal age of >45 years; (iv) Women with POI compared with those with menopausal age of 45-55 years; (v) Women with late menopause compared with those with menopausal age of 45-55 years.

Risk of bias and study quality assessment

Newcastle-Ottawa scale (NOS) was used for assessing the quality of each study. Briefly, this system evaluates studies based on three criteria: (i) Participant selection; (ii) Comparability of study groups, and (iii) Assessment of outcome or exposure. A study can be awarded a maximum of four stars for the selection category, a maximum of two stars for the comparability category and a maximum of three stars for the outcome / exposure category [17]. These results are available in Supplementary Table 2.

Statistical analyses

Heterogeneity was tested with the Cochrane chi-square test and the degree of heterogeneity was quantified by the I^2 statistics. An I^2 of 30-60% was considered as

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moderate, whereas values >60% were considered as high degree of heterogeneity. Random effects model was used for data synthesis. Associations were reported as odds ratios (OR) with their 95% confidence intervals (CI). A *p* value of <0.05 was considered as statistically significant. Publication bias was formally tested with Begg-Mazumdar test (presented in funnel plot diagram, with *p* values >0.1 indicating absence of publication bias) and the Egger's test (*p* values >0.1 indicating absence of publication bias). All analyses were done with the software *Comprehensive MetaAnalysis V2*.

Results

Descriptive data

The initial search provided 1,851 results, after excluding duplicates, 19 of which were assessed as full texts for eligibility (Figure 1). Of those, six articles were excluded, due to the following reasons: (i) No data on T2DM according to menopausal age (n=1); (ii) No data on EM (n=3); (iii) Non-English language (n=1); (iv) Referral to another paper already included in the analysis (n=1). Thirteen studies were included in the qualitative and quantitative analysis [11-14, 18-26]. The excluded studies and the reasons for their exclusion are available in Supplementary Table 3. The studies were published between 2013 and 2017. The countries in which they were conducted were: China (n=5), USA (n=2), India (n=1), Japan (n=2), Vietnam (n=1) and Netherlands (n=1). One study was conducted in more than one country (in Europe). The number of participants ranged from 100 to 124,379, yielding a total number of 191,762 postmenopausal women, with 21,664 cases of T2DM. The mean age of participants was 62.6±7.6 years (data available from nine studies) and mean BMI was 23.9±3.8 kg/m^2 (data available for seven studies).

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Diagnosis of T2DM was set by various methods. Fasting plasma glucose (FPG) ≥126 mg/dl (7 mmol/l) or glycated hemoglobin (HbA_{1c}) ≥6.5% or plasma glucose ≥200 mg/dl (11.1 mmol/l) at 2 hours, after an oral glucose tolerance test (OGTT) were used in eight studies [12, 14, 18, 21, 22, 24-26]. Of note, in one study OGTT was performed with a glucometer [20] and in another study the method of T2DM diagnosis was not defined [13]. In the remaining studies, the diagnosis was derived from self-reports, health care reports, hospital admissions or history of anti-diabetic medication use [11, 19, 23]. With respect to the type of menopause, five studies included only women with natural menopause [12, 13, 22, 24-26], four included mixed populations (9-39% of which with surgical menopause) [11, 14, 18, 19, 23] and in three studies [20-22] the type of menopause was not clearly defined. No data on prediabetes (defined either as "impaired fasting glucose" or "impaired glucose tolerance") were available. The descriptive characteristics of the studies' participants are presented in Tables 1 and 2.

Comparison of women with EM with those with normal menopausal age

Women with EM displayed a higher risk of developing T2DM compared with women with normal menopausal age (>45 years) including also those with late menopausal age (12 studies, four prospective cohorts) [11-14, 18, 19, 21-26] (OR: 1.12, 95% CI: 1.01-1.23, p=0.019; I^2: 65.69%, p<0.001). One study did not provide absolute number of participants in both T2DM and non- T2DM groups and, therefore, OR was directly included in the analysis [20] (Figure 2).

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Compared with women with menopausal age of 45 - 55 years, women with EM were also at a higher risk for T2DM (13 studies, four prospective cohorts) (OR: 1.15, 95% CI: 1.04-1.26, p=0.003; I^2: 61%, p<0.002)] [11-14, 18-26] (Figure 3). A variation with respect to the upper limit of normal menopausal age must be noted (ranging from 49 to 55, mostly 52-55). After excluding three studies having used the age of 49 or 50 years as the upper limit of normal menopausal age, the OR of the remaining studies remained significant (1.13, 95% CI: 1.03-1.24, p=0.008) [13, 18, 20].

Comparison of women with POI with those with normal menopausal age

Women with POI demonstrated a higher risk for developing T2DM compared with women with normal menopausal age, including those with late menopausal age (five studies, three prospective cohorts) (OR: 1.53, 95% CI: 1.03-2.27, p=0.035; I^2: 78%, p<0.001) [9, 11, 13, 19, 22] (Figure 4). Compared with women with menopausal age of 45 - 55 years, women with POI were also at a higher risk of T2DM (five studies, three prospective cohorts) (OR: 1.50, 95% CI: 1.03-2.19, p=0.033; I^2: 75.2%, p<0.003)] [9, 11, 13, 19, 22] (Figure 5). The upper limit of normal menopausal age was defined at 49-55 years.

Late menopause

We also investigated for a potential difference between late menopause and normal menopausal age (45-55 years) with respect to T2DM risk (ten studies, four cohorts) [11, 12, 14, 19, 21-26]. A tendency for a higher risk of T2DM was observed for women with late menopausal age (OR: 1.12, 95% CI: 0.99-1.28, p=0.069; I^2: 75.1%, p<0.001).

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Meta-regression analysis

Mean age of the participants at study entry, BMI, smoking status and level of physical activity were used as predictors of T2DM development. Mean age of the participants appeared to significantly contribute to the impact of the age at menopause on T2DM risk (Q: 7.62, df: 1, p=0.006) (Figure 6). There was no evidence that BMI altered the effect of age at menopause on the risk of T2DM. Meta-regression analysis for smoking status and physical activity was not possible due to the small number of studies or different ways of definition.

Subgroup analysis

Subgroup analysis was performed with regard to race (Asian versus non-Asian populations), type of menopause (surgical versus natural), study design (cohorts versus case-control studies) and the use of hormone replacement therapy (HRT) and / or oral contraceptives (OC). All subgroup analyses were performed in the concept of comparison between women with EM and those with natural menopause (age at menopause 45-55 years) (13 studies). Non-Asian women with EM were still at a higher risk of T2DM compared with those with natural menopause of the same race (OR: 1.25, 95% CI: 1.11-1.41, p<0.001), whereas no such risk was observed for Asian populations (OR: 1.06, 95% CI: 0.92-1.22, p=0.392). However, there was no difference between these two subgroups (p=0.082). The same associations were observed according to the type of study, being significant only for cohort studies (p < 0.001), with no significant between-group heterogeneity (p = 0.082). Furthermore, no difference was detected according to the use of HRT and/or OC (p=0.773). With respect to the type of menopause, no

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subgroup analysis could be conducted, since no distinct data on surgical menopause were available.

Discussion

To the best of our knowledge, this systematic review and meta-analysis including, 191,762 postmenopausal women and 21,664 cases of T2DM, is the first regarding the association between age of menopause and risk of developing T2DM. Both EM and POI are associated with a higher risk of developing T2DM compared with women with natural menopause, an association that was partially affected by age but not BMI. A tendency for a higher risk was also found for women reporting menopause after 55 years of age.

The exact pathogenetic mechanisms underlying the association between premature menopause and T2DM risk cannot be fully elucidated. A possible mechanism is the shorter exposure to endogenous estrogens, taking into consideration the protective role of estrogens on pancreatic β-cell function and insulin resistance. Estradiol, through binding to its receptor alpha (ERα) in β-cells and through the concomitant phosphorylation of extracellular signal-regulated kinases (ERK1/2), regulates insulin biosynthesis and secretion and modulates β-cell survival [27]. EM- or POI-associated glucose intolerance may also be an indirect effect of the metabolic consequences of body fat redistribution due to estrogen deficiency, which leads to increased central adiposity, predisposing to increased insulin resistance [28, 29]. Moreover, menopause-related changes in serum concentrations of other steroid hormones, such as testosterone, as well as those of sex

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hormone binding globulin (SHBG), may also play a role in the development of T2DM. Testosterone production by the ovaries is reduced to a lesser extent after menopause, compared with that of estradiol (30% versus 80%) [30, 31]. On the other hand, SHBG seems to be protective against T2DM, since its low concentrations have been associated central adiposity and insulin resistance [30, 31]. Interestingly, a meta-analysis showed that postmenopausal women with T2DM have higher total testosterone and lower SHBG concentrations compared with those without T2DM. In particular, SHBG concentrations >60 nmol/L confer a lower risk of T2DM (RR: 0.20, 95% CI: 0.12-0.30)], compared with concentrations ≤60 nmol/L [30].

The main clinical implication of the present study is the identification of women with EM or POI as a group at higher risk of T2DM and at an earlier stage, especially when other risk factors co-exist (e.g. positive family history for T2DM). In these women, an earlier cautiousness and intensification of lifestyle intervention compared with the general population could be of value. Another clinical implication is the beneficial effect of HRT on glucose metabolism in women with EM or POI [32]. Data from large interventional studies, such the Women's Health Initiative (WHI) [33] and the Heart and Estrogen/progestin Replacement Study (HERS) [34], have shown a decreased risk of T2DM (21-35%, after 4.1 or 5.6 years of treatment) with the use of HRT (conjugated estrogen 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d) compared to placebo. Notably, this effect was independent of waist circumference or BMI. Current guidelines support a beneficial effect of HRT on T2DM risk, which involves a reduction by 14-19%. This effect does not seem to persist after HRT discontinuation [35].

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On the other hand, exposure to excessive estrogen plays also a detrimental role in β-cell function, since it leads to overstimulation of ERα, resulting in excessive insulin signaling and, eventually, insulin resistance in liver and muscle [27]. In a meta-analysis of 13 population-based prospective studies, high concentrations of total estradiol were associated with increased risk of T2DM [36]. This may partly explain the tendency of increased T2DM risk in women with menopausal age >55 years, supporting the notion of a U-shape pattern of the effect of estrogen concentrations and duration of exposure on glucose metabolism. Surprisingly, increased body weight seems to be associated with a later age at menopause, which may also explain the tendency of association between late menopause and increased T2DM risk [37, 38] The effect of other sex steroid hormones, such as testosterone, on the age at menopause seems to be negligible [19, 36], although others have shown an effect of increased androgen concentrations on higher T2DM risk during menopause [39]. The aforementioned meta-analysis showed that postmenopausal women with T2DM have higher estradiol concentrations, compared with those without [30] .

Another plausible explanation of the positive association between premature menopause and T2DM could be the co-existence of risk factors that predispose to both conditions, such as smoking, low physical activity, obesity and socioeconomic status. Smoking, a well-known risk factor for T2DM [40], has been also associated with a reduction in time to menopause [37] [38], a decrease in size of the ovarian follicle pool [41] and an increase in follicle stimulating hormone (FSH) concentrations [42]. Toxic chemicals released by tobacco use, such as polycyclic aromatic hydrocarbons, may lead to apoptosis of oocytes

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[43]. Unfortunately, we could not perform meta-regression analysis on this parameter, due to insufficient and heterogeneous data regarding the definition and classification of smoking habit in the included studies. Furthermore, low socio-economic status and education are associated with both higher prevalence of T2DM [44] and earlier age at menopause [37]. Conflicting data exist with regard to physical activity, since low physical activity has been associated with both later [37] and earlier [38] age at menopause.

Genetic variants may predispose to an earlier age of the FMP, since they account for approximately 50% of the variation in the age at menopause [45]. Polymorphisms in genes implicated in DNA repair (such as XO1, HELQ, UIMC1, FAM175A, FANCI, TLK1, POLG, PRIM1) and immune function (such as IL11, NLRP11, BAT2) have been associated with an earlier timing of menopause [46]. Whether these polymorphisms predispose to T2DM risk or just to premature aging is unknown. Some DNA repair gene polymorphisms, such as Xeroderma pigmentosum complementation group D (XPD) and human oxoguanine glycosylase 1 (hOGG1), have been recognized as potential mediators in the pathogenesis of T2DM [47]. Mitochondrial dysfunction seems to play a role both in the timing of menopause [46] and the pathogenesis of T2DM [48]. The obscure contribution of a potential genetic predisposition in earlier menopausal age is further supported by the fact that both race and ethnicity do not seem to be significantly associated with the age of menopause in other studies [37]. In general, age at the natural menopause is a result of constellation of both genetic and environmental factors [37] and clear causality cannot be supported by the aforementioned associations. The tendency for an association between

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late menopause and increased T2DM risk may be partly attributed to age-related metabolic disturbances, such as central obesity and insulin resistance.

The present study has certain limitations. First, the different design of the original studies might have contributed to the relatively high degree of heterogeneity. The main drawback with case-control studies is that they could not ascertain T2DM, the latter being a self-reported diagnosis. However, the meta-analysis includes four cohort-studies, with a follow-up time between 8-10 years; the significance in the results remained after performing a subgroup analysis. Second, the diagnosis of T2DM was set with different methodology in the studies included. However, after performing a separate analysis for the studies that used either FPG, OGTT or HbA_{1c} concentrations, the association between EM and T2DM remained significant (eight studies); the same was not true for the association between POI and T2DM (two studies). Third, past use of HRT or OC was not reported in five studies. Of note, the percentage of the participants having received HRT or OC was relatively low and the exact duration could not be defined in most studies. Therefore, it is probable that it did not alter the results, taking also into account the fact that in the remaining eight studies, subgroup analyses did not demonstrate such an effect. Fourth, in most subjects included, the age of natural menopause was self-reported (defined as 12 months of amenorrhea), which was subjected to recall bias and the nature of cross-sectional design. Moreover, the cause of EM, which may include chemoradiation or oophorectomy, may have had an independent impact on the risk of T2DM. Unfortunately, no data were available on the exact cause of EM and its impact on T2DM. Therefore, no subgroup analysis could be performed on this regard. Fifth, we did not use

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(age-adjusted or unadjusted) OR directly from the included studies. Only absolute numerical data were extracted, except for the study by Binh *et al.* [20], to perform comparisons between T2DM and non-T2DM cases in women with EM and normal menopause.

Conclusions

In summary, this systematic review and meta-analysis in postmenopausal women shows that women entering menopause at an earlier age (either <45 or <40 years) have an increased risk of developing T2DM compared with those with menopausal age >45 years. This should be taken into account in building prognostic models to early detection of T2DM in women, especially in those at high risk status, to necessitate lifestyle intervention strategies and potential pharmaceutical therapy. Well-designed, prospective cohort and interventional studies will further elucidate these issues.

Declaration of interest

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Authors' contributions

PA designed the research, extracted and analyzed the data and wrote the first draft of the paper. KC, AMA, NKG, NK, and PS searched the literature, extracted and analyzed the data. KC was responsible for the statistical analysis and reviewed the manuscript. SAP, MP, ET, EK, IL and JCS reviewed the manuscript and provided critical scientific input. DGG resolved discrepancies regarding the quality of the studies included in the meta-analysis, provided critical scientific input and had the primary responsibility for the paper's final content.

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Figure legends

Figure 1. Flow chart diagram

Figure 2. Forest plot of the comparison between early menopause (EM) and menopause >45 years

Figure 3. Forest plot of the comparison between early menopause (EM) and menopause at 45-55 years

Figure 4. Forest plot of the comparison between premature ovarian insufficiency (POI) and menopause >45 years

Figure 5. Forest plot of the comparison between premature ovarian insufficiency (POI) and menopause at 45-55 years

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Figure 6. Meta-regression analysis of the effect of age on the association of premature menopause with increased risk of type 2 diabetes

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Table 1. Demographic characteristics of studies included in the analysis

Study characteristics					Characteristics of the participants				Type of menopause	
Id	**First author, Year of publication**	**Study design**	**Total number**	**Women with T2DM**	**Use of HRT, n (%)**	**Use of OC, n (%)**	**Mean age (years)**	**BMI (kg/m^2)**	**Natural, n (%)**	**Other, n (%)**
1.	Mahajan, 2012	Case-Control	100	6	N/A	N/A	N/A	N/A	100 (100)	0 (0)
2.	Brand, 2013	Cohort	7,864	3,691	1,292 (29) *	1,792 (40) *	59.2 ± 5.8	26.3 ± 4.6	3,550 (78) *	858 (22) *
3.	Lee, 2013,	Case-Control	4,318	140	603 (14)	N/A	53.5 ± 3.3	22.6 ± 2.8	4,318 (100)	0 (0)
4.	Qiu, 2013	Case-Control	3,304	738	N/A	N/A	59.4 ± 8.2	24.3 ± 3.2	3,003 (90)	301 (10)
5.	Heianza, 2013	Case-Control	4,416	170	N/A	N/A	57.1 ± 6.6	21.8 ± 3.0	3,552 (78)	1,018 (22)
6.	Appiah, 2014	Cohort	2,597	176	797 (30)	532 (20)	60.7 ± 10.7	N/A	1,562 (60)	1,035 (40)
7.	Binh, 2015	Case-Control	608	46	N/A	N/A	N/A	N/A	N/A	N/A
8.	Fu, 2016	Case-Control	2,099	394	N/A	N/A	66.1 ± 4.8	N/A	N/A	N/A
9.	LeBlanc, 2016	Cohort	124,379	11,262	74,133 (59)	52,898 (42.5)	63.4 ± 7.2	N/A	98,871 (79.5)	25,508 (20.5)
10.	Yang, 2016	Case-Control	5,063	640	194 (3.8) **		59.2 ± 7.9	24.2 ± 3.3	N/A	N/A
11.	Muka, 2017	Cohort	3,639	348	95 (2.6)	N/A	66.9 ± 9.6	27.0 ± 4.4	3,639 (100)	0 (0)
12.	Shen, 2017	Case-Control	16,299	2,811	369 (2)	2,906 (18)	63.6 ± 8.3	24.2 ± 3.5	16,299 (100)	0 (0)
13.	Wang, 2017	Case-Control	17,076	1,288	N/A	3,186 (18)	59.0 ± 6.7	22.8 ± 3.4	17,076 (100)	0 (0)

Data are presented as mean ± SD or n (%).

Abbreviations: T2DM: type 2 diabetes mellitus; HRT: hormone replacement therapy; OC: oral contraceptives; BMI: body mass index;

FPG: fasting plasma glucose, OGTT: oral glucose tolerance test; N/A: not available

* number refers to a sub-cohort of 4,408 participants.

** number refers to HRT and / or OC users.

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Table 2. Number of participants according to the age of menopause

Id	First author, Year	Number of participants according to the age of menopause (years)											
		< 40		< 45		> 45		45 – [52 – 55]		≥ 50		≥ [52 – 55]	
		Total	T2DM	Total	T2DM	Total	T2DM	Total	T2DM	Total	T2DM	Total	T2DM
1.	Mahajan, 2012	8	2	50	3	50	3	31	1	19	2		
2.	Brand, 2013	419	220	1,306	644	6,558	3,047	5,903	2,740	3,988	1,861	655	307
3.	Lee, 2013			305	6	4,013	134	3,710	122			303	12
4.	Qiu, 2013			671	146	2,633	592	2,022	451	1,820	425	611	141
5.	Heianza, 2013			660	29	3,756	141	1,290	43	2,466	98		
6.	Appiah, 2014	457	52	865	78	1,732	98	1,551	91	1,037	60	181	7
7.	Binh, 2015												
8.	Fu, 2016			351	69	1,753	325	1,464	250			284	75
9.	LeBlanc, 2016			34,922	3,523	89,457	7,739	72,720	6,189			16,737	1,550
10.	Yang, 2016	349	40	1,253	142	3,810	498	3,638	461	1,373	198	172	37
11.	Muka, 2017	83	15	381	54	3,258	294	3,015	280	243	14	243	14
12.	Shen, 2017			2,027	401	14,272	2,410	11,863	2,024			2,409	386
13.	Wang, 2017			1,733	125	15,343	1,163	12,991	948			2,352	215

T2DM: type 2 diabetes mellitus.

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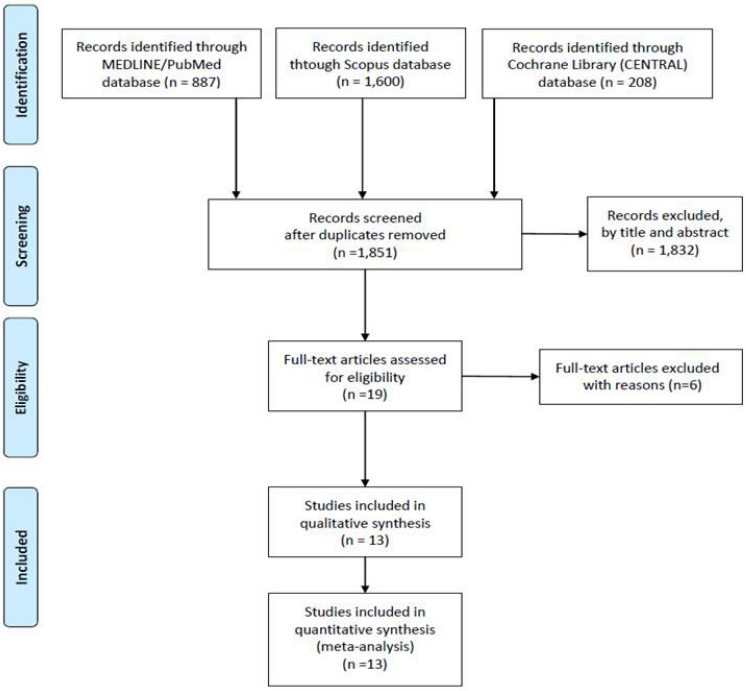

Figure 1.

Figure 1. Flow chart diagram

254x190mm (96 x 96 DPI)

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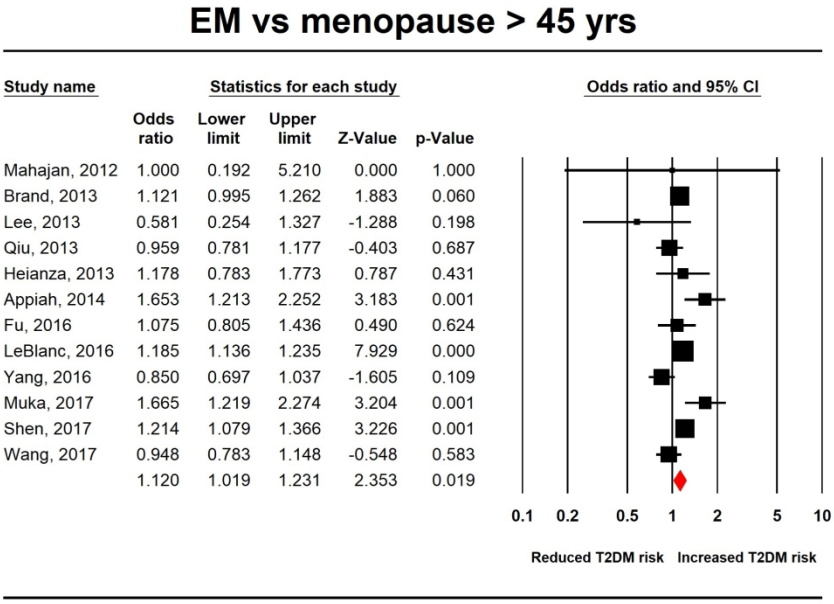

Figure 2. Forest plot of the comparison between early menopause (EM) and menopause >45 years

448x336mm (130 x 130 DPI)

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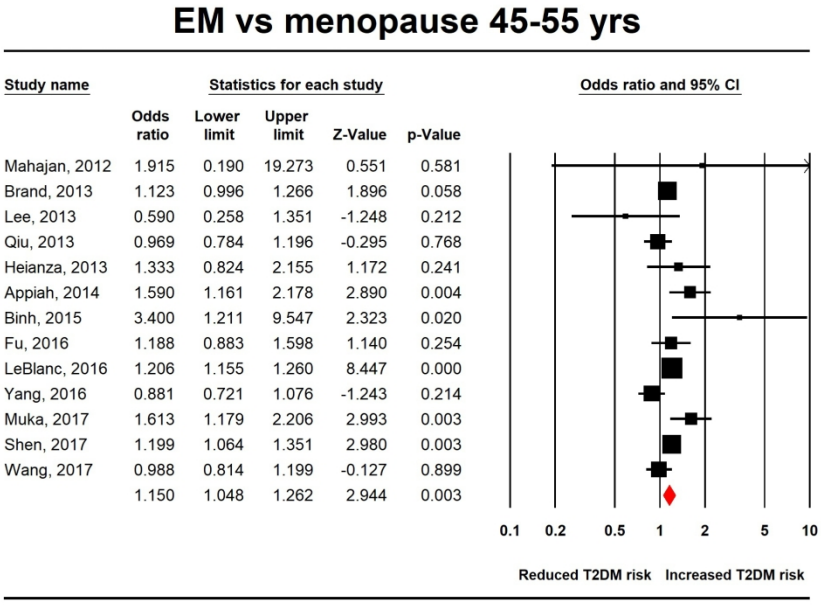

Figure 3. Forest plot of the comparison between early menopause (EM) and menopause at 45-55 years

448x336mm (130 x 130 DPI)

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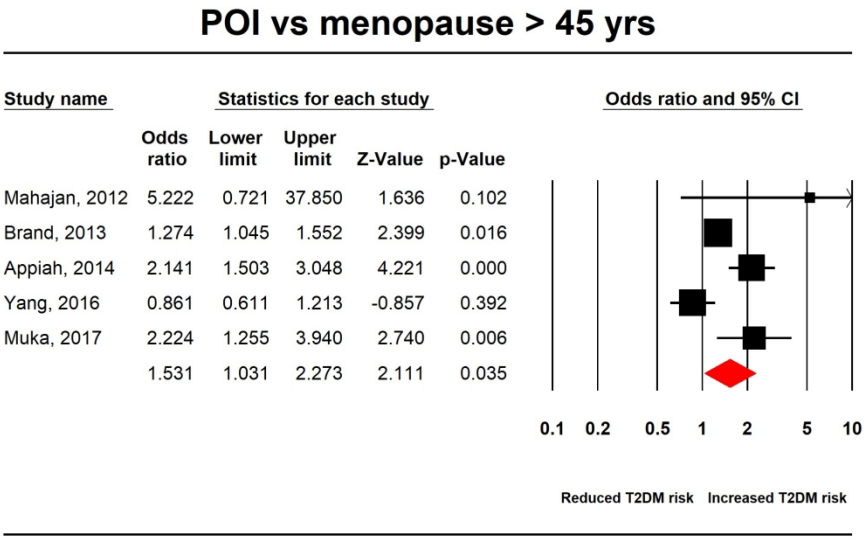

Figure 4. Forest plot of the comparison between premature ovarian insufficiency (POI) and menopause >45 years

448x336mm (130 x 130 DPI)

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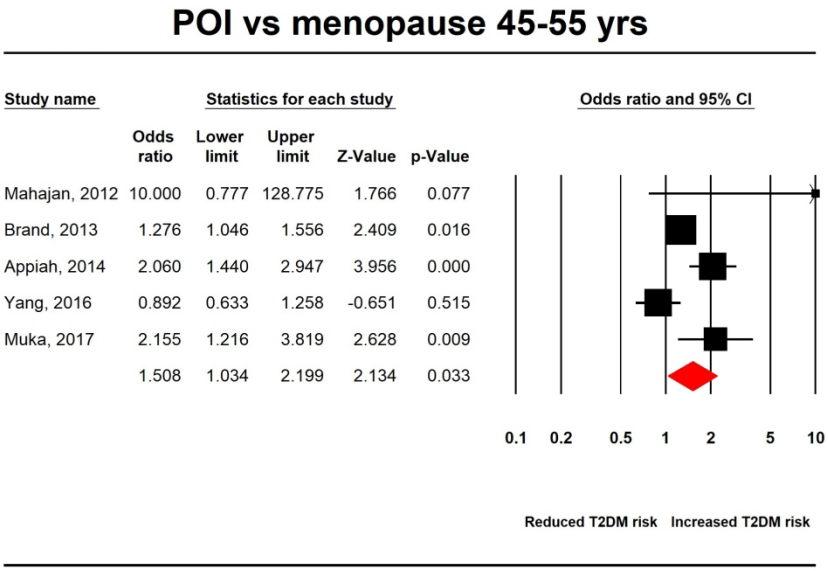

Figure 5. Forest plot of the comparison between premature ovarian insufficiency (POI) and menopause at 45-55 years

448x336mm (130 x 130 DPI)

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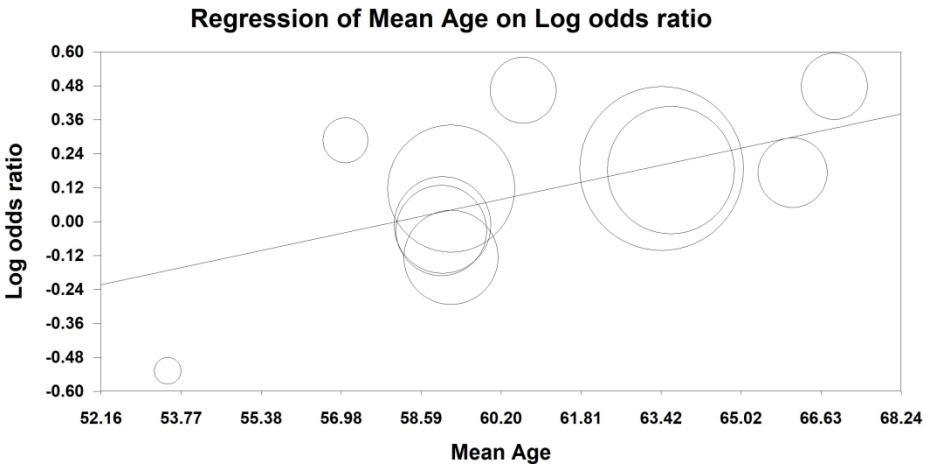

Figure 6. Meta-regression analysis of the effect of age on the association of premature menopause with increased risk of type 2 diabetes

564x273mm (130 x 130 DPI)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3 – 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5 – 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	n/a
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8 - 9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8 - 9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 -10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 - 10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11 -13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11 - 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11 -13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11 -13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12 -13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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Supplementary table S2. Study quality as assessed by the Newcastle-Ottawa scale.

Id	First author, Year	Selection	Comparability	Exposure / Outcome	Overall quality
1.	Mahajan, 2012	1	1	1	Fair
2.	Brand, 2013	4	2	3	Good
3.	Heianza, 2013	4	2	2	Good
4.	Lee, 2013	4	2	2	Good
5.	Qiu, 2013	4	2	3	Good
6.	Appiah, 2014	4	2	3	Good
7.	Binh, 2015	3	2	1	Fair
8.	Fu, 2016	4	2	2	Good
9.	Yang, 2016	4	2	2	Good
10.	LeBlanc, 2017	4	2	3	Good
11.	Muka, 2017	4	2	3	Good
12.	Shen, 2017	4	2	2	Good
13.	Wang, 2017	3	2	2	Good

According to the Newcastle-Ottawa scale, a study can be awarded a maximum of four stars for the selection category, a maximum of two stars for the comparability category and a maximum of three stars for the outcome/exposure category.

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Supplementary table S3. Full-text articles excluded from data synthesis.

Study	**Year**	**Reasons for exclusion**	**Number of studies**
Lisabeth et al.	2009	No data on diabetes according to menopausal age	1
Di Donato et al.	2005	No data on early menopause	3
Kim et al.	2011		
Lejskova et al.	2014		
Wen et al.	2017	Non-English language	1
Nursing Standard Journal	2017	Referring to another article already included for analysis	1

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